Available online at www.sciencedirect.com
ScienceDirect
Tetrahedron Letters
Tetrahedron Letters 48 (2007) 1695–1698

Carbon–bromine cleavage by dimethyl sulfoxide: the key step of C(5) functionalization of push–pull 2-alkylidene-4-oxothiazolidine vinyl bromides

Marija Baranac Stojanović* and Rade Marković

Faculty of Chemistry, University of Belgrade, Studentski trg 16, PO Box 158, 11001 Belgrade, Serbia
Center for Chemistry ICTM, PO Box 473, 11000 Belgrade, Serbia

Received 16 October 2006; revised 27 December 2006; accepted 10 January 2007
Available online 14 January 2007

Abstract—Push–pull 2-alkylidene-4-oxothiazolidine vinyl bromides undergo efficient C(5) functionalization through DMSO-assisted carbon–bromine cleavage, followed by a bromine transfer-substitution (or elimination) sequence. A mechanism for this novel transformation is proposed.

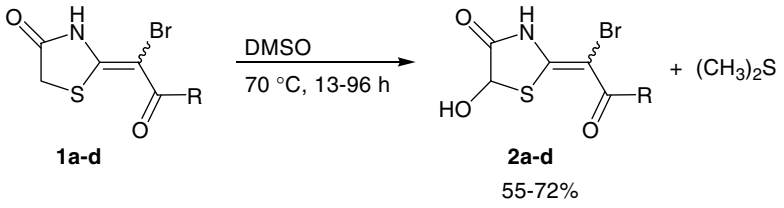
Dimethyl sulfoxide (DMSO) is widely used in organic synthesis, both as a solvent and as a reagent. Numerous reactions based on DMSO as the reagent have been the subject of several reviews.[1–4] For example, oxidation of halides and tosylates to aldehydes or ketones, thiols to disulfides, sulfides to sulfoxides, primary and secondary hydroxy groups to the corresponding carbonyl groups in a variety of compounds, and preparation of sulfilimines and sulfoximines, are all important reactions in which DMSO is employed either as the sole reagent or in a combination with other reagents. Combined with *N*-bromosuccinimide, it can be used for the synthesis of α-bromo alcohols from alkenes,[5,6] methylene acetals from alcohols,[7] or for the oxidation of 1,2-diarylethanones to diarylethanediones.[8] Recently, a mixture of NBS and DMSO has been applied for the oxidation of nucleoside phosphite to phosphate, as a step in the synthesis of oligonucleotides.[9] In combination with alkyl halides, DMSO is applied for halogenation of aromatic compounds,[10] aldehydes and ketones,[11] and quinones.[12] The mixture, DMSO/$(COCl)_2$, can dehydrate amides to nitriles,[13] whereas alkylarenes are oxidized to arylketones with polyoxomolybdates in DMSO.[14] A recently reported catalyst-free synthesis of cyanohydrin carbonates from aldehydes was promoted by DMSO.[15] In addition, DMSO–iodine can be used for deallylation of a variety of allylic carboxylic esters,[16] while a DMSO–iodine–CuO system has been employed for C–C double bond formation from aryl or heteroaryl methyl ketones.[17]

Despite the number and diversity of these reactions, most frequently based on attack by the nucleophilic oxygen of DMSO on electrophilic centers to form reactive sulfonium salts,[18–21] the ability of DMSO to initiate a specific reaction by halogen abstraction from vinyl halides has not yet been reported. Herein, we report the first application of DMSO as a reactant for the C(5) functionalization of push–pull 2-alkylidene-4-oxothiazolidine vinyl bromides, involving bromine abstraction by DMSO as a key step, followed by a bromine transfer-substitution (or elimination) sequence. Thus, treatment of vinyl bromides[22] **1a–d**, which belong to the class of synthetically useful α-acylvinyl anion equivalents,[23,24] with wet DMSO at 70 °C resulted, after prolonged reaction time, in the formation of new 5-hydroxy vinyl bromides **2a–d**, in good yields (Scheme 1, Table 1, entries 1–4).[25]

Under similar reaction conditions, vinyl bromides **3a–d**, possessing the ethoxycarbonylmethyl substituent at the C(5) position, were oxidized to 5-ethoxycarbonylmethylidene derivatives **4a–d**, in high yields (Scheme 2, Table 1, entries 5–8).

Keywords: Push–pull 2-alkylidene-4-oxothiazolidines; Vinyl bromides; Dimethyl sulfoxide; C(5) Functionalization.
* Corresponding author. Tel.: +381 11 3336 740; fax: +381 11 636 061; e-mail: mbaranac@helix.chem.bg.ac.yu

0040-4039/$ - see front matter © 2007 Elsevier Ltd. All rights reserved.
doi:10.1016/j.tetlet.2007.01.051



Scheme 1.

Table 1. Synthesis of 5-hydroxy-4-oxothiazolidine vinyl bromides **2a–d** and 5-ethoxycarbonylmethylidene-4-oxothiazolidine vinyl bromides **4a–d**

Entry	Compound[a]	R	Mp (°C)	Yield[b] (%)
1	*Z*+*E*-**2a**	NHPh	136	63
2	*Z*+*E*-**2b**	$NHCH_2CH_2Ph$	111–113	72
3	*Z*+*E*-**2c**	OEt	105	55
4	*Z*+*E*-**2d**	Ph	100–102	55
5	2*Z*,5*Z*+2*E*,5*Z*-**4a**	NHPh	185–187	85
6	2*Z*,5*Z*+2*E*,5*Z*-**4b**	$NHCH_2CH_2Ph$	154–155	93
7	2*Z*,5*Z*+2*E*,5*Z*-**4c**	OEt	184–187	79
8	2*Z*,5*Z*+2*E*,5*Z*-**4d**	Ph	147	98

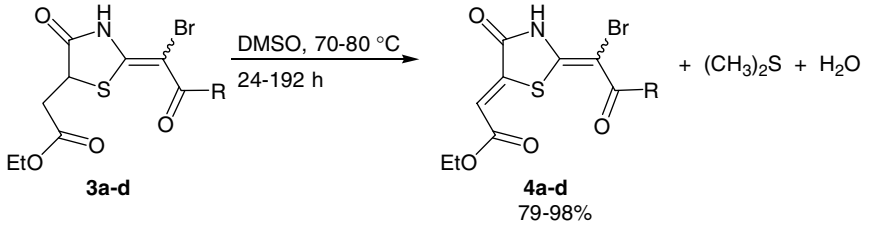
[a] All compounds gave satisfactory elemental analysis and ^1H NMR, ^{13}C NMR, and MS spectra.
[b] Yield of product after purification by chromatography.

It should be noted that in a control experiment, carried out under an argon atmosphere in degassed DMSO, **1a** was hydroxylated to **2a** in almost identical yield (59%), as in the reaction carried out under aerobic conditions (Table 1, entry 1), which excludes possible oxidation by aerial oxygen.

In order to gain additional information, the slow, albeit efficient C(5) functionalization of vinyl bromides **1a** and **1d** to **2a** and **2d**, respectively, was monitored by ^1H NMR spectroscopy in DMSO-d_6 at room temperature. In particular, starting from precursor **1a**, besides final product **2a**, parent 4-oxothiazolidine **5a** was formed as an intermediate (Table 2).

In the recently reported pyridinium hydrobromide perbromide (PHBP) bromination-rearrangement of 2-alkylidene-5-ethoxycarbonylmethyl-4-oxothiazolidine derivatives[26] we proposed that a vinyl bromide intermediate of type **3** undergoes a pyridine-assisted heterolytic cleavage of the C–Br bond en route to the final products. In this sense, the most important structural difference between the typical, relatively unreactive vinyl bromides **7** and vinyl bromides such as **1a–d** and **3a–d**, depicted by general structure **8**, in which bromine is attached to the C–C double bond exhibiting push–pull character, has to be noted (Fig. 1).

Whereas resonance stabilization in **7**, involving bromine and the double bond, makes the C–Br bond stronger



Scheme 2.

Table 2. Mol percentage[a] of **1a**, **2a**, **5a** and **6a** in DMSO-d_6 as a function of time

Entry	Reaction time (days)	**1a**	**2a**	**5a**	**6a**[b]
1	Initial	100	0	0	0
2	2	86	9	4	1
3	3	76	17	5	2
4	6	45	42	6	7
5	10	12	69	4	15
6	13	Traces	80	0	20

[a] Determined by integration of the hydrogen atom signals of C-5 in **1a** and **2a** and the vinyl hydrogens in **5a** and **6a**.
[b] Also formed from **2a** after prolonged standing in wet DMSO.

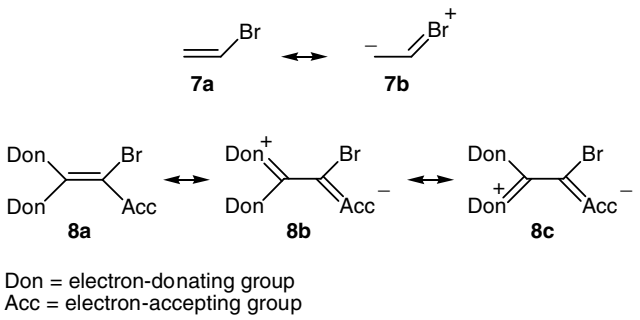


Figure 1.

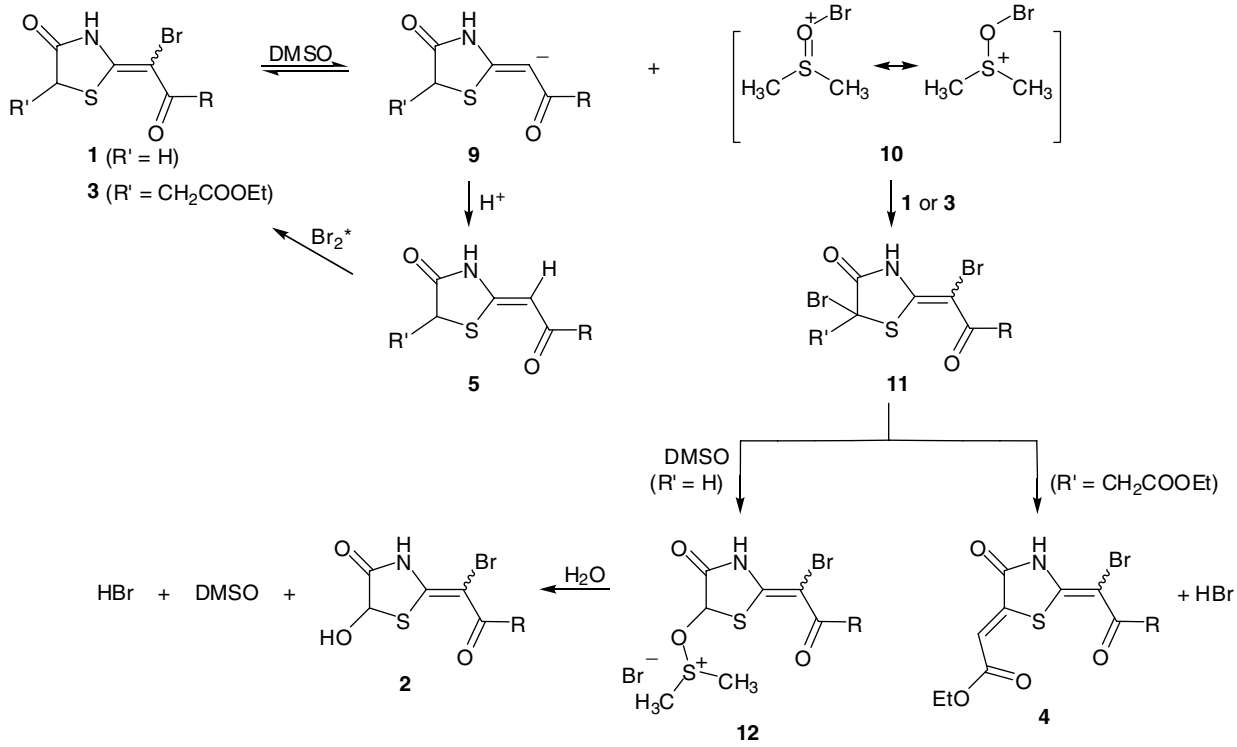
and less reactive, resonance stabilization of the Don–C=C–Acc moiety of **8**, characteristic for push–pull alkenes,[27] weakens electronic interaction between bromine and the double bond, making the C–Br bond in bromides **8** susceptible to heterolytic cleavage.[28] These key features, which profoundly influence the reactivity of precursors **1** and **3**, supported by the known chemical behavior of DMSO, lead us to propose the following mechanistic pathway for the described reactions (Scheme 3).

In the first step, highly polar DMSO induces ionization of vinyl bromides **1** and **3**, resulting in the formation of carbanion **9** and DMSO–bromonium type species **10**, stabilized by the distribution of the positive charge on sulfur. Protonation of **9** by water, present in sufficient amount in DMSO (vide infra), yields the observed 4-oxothiazolidine intermediate **5**. Once formed, cation **10** reacts with another molecule of vinyl bromide **1**, or **3** giving dibromide **11**. When $R' = H$, the next step is the formation of the expected alkoxydimethylsulfonium salt **12**. Decomposition of alkoxydimethylsulfonium salts to carbonyl compounds, usually in the presence of a base, is a well-known reaction.[29–31] In this case, however, an efficient hydrolysis to the final alcohol **2** and DMSO occurs, with simultaneous HBr release.[32] In the case of $R' = CH_2COOEt$, HBr elimination leads to the stable, conjugated products **4**. The liberated HBr reacts with DMSO to form molecular bromine,[33,34] Eq. 1, which brominates the intermediate 4-oxothiazolidine **5**, yielding the starting vinyl bromides **1**, or **3** which reenter the reaction cycle.

$$2\,HBr + CH_3S(=O)CH_3 \longrightarrow Br_2 + CH_3SCH_3 + H_2O \quad (1)$$

Although, the water necessary for the reaction (Scheme 3) is formed in this redox step, the amount necessary to initiate the reaction was already present in DMSO.[35]

In conclusion, we have developed a method for the introduction of a new functionality, that is, a hydroxy group or C–C double bond, into the C(5) position of 5-unsubstituted and 5-substituted-4-oxothiazolidine vinyl bromides, respectively. The method is based on the propensity of thiazolidinone vinyl bromides to undergo bromine transfer from the exocyclic C=C bond to the C(5) position of the ring[36,37] and the ability of DMSO to initiate this process by C–Br cleavage and to oxidize bromide to molecular bromine.



*Formed by the oxidation of liberated HBr with DMSO (see equation 1).

Scheme 3.

Acknowledgment

Partial financial support by the Ministry of Science of the Republic of Serbia, Grant No. 142007 (to R.M.) is acknowledged.

References and notes

1. Epstein, W. W.; Sweat, F. W. *Chem. Rev.* **1967**, *67*, 247–260.
2. Butterworth, R. F.; Hanessian, S. *Synthesis* **1971**, 70–88.
3. Mancuso, A. J.; Swern, D. *Synthesis* **1981**, 165–185.
4. Tidwell, T. T. *Synthesis* **1990**, 857–870.
5. Dalton, D. R.; Hendrickson, J. B.; Jones, D. *J. Chem. Soc., Chem. Commun.* **1966**, 591–592.
6. Dalton, D. R.; Dutta, V. P.; Jones, D. C. *J. Am. Chem. Soc.* **1968**, *90*, 5498–5501.
7. Hanessian, S.; Yang-Chung, G.; Lavallee, P.; Pernet, A. G. *J. Am. Chem. Soc.* **1972**, *94*, 8929–8931.
8. Tatsugi, J.; Izawa, Y. *J. Chem. Res. (S)* **1988**, 356–357.
9. Uzagare, M. C.; Padiya, K. J.; Salunkhe, M. M.; Sanghvi, Y. S. *Bioorg. Med. Chem. Lett.* **2003**, *13*, 3537–3540.
10. Dossena, A.; Marchelli, R.; Casnati, G. *J. Chem. Soc., Perkin. Trans. 1* **1983**, 1141–1144.
11. Armani, E.; Dossena, A.; Marchelli, R.; Casnati, G. *Tetrahedron* **1984**, *40*, 2035–2039.
12. Kallmayer, H.-J.; Burgardt, S.; Doerr, M. *Scientia Pharmaceutica* **1996**, *64*, 25–30.
13. Nakajima, N.; Saito, M.; Ubukata, M. *Tetrahedron* **2002**, *58*, 3561–3577.
14. Khenkin, A. M.; Neumann, R. *J. Am. Chem. Soc.* **2002**, *124*, 4198–4199.
15. Iwanami, K.; Hinakubo, Y.; Oriyama, T. *Tetrahedron Lett.* **2005**, *46*, 5881–5883.
16. Taksande, K. N.; Sakate, S. S.; Lokhande, P. D. *Tetrahedron Lett.* **2006**, *47*, 643–646.
17. Yin, G.; Zhou, B.; Meng, X.; Wu, A.; Pan, Y. *Org. Lett.* **2006**, *8*, 2245–2248.
18. Nace, H. R.; Monagle, J. J. *J. Org. Chem.* **1959**, *24*, 1792–1793.
19. Albright, J. D.; Goldman, L. *J. Am. Chem. Soc.* **1967**, *89*, 2416–2423.
20. Mancuso, A. J.; Huang, S.-L.; Swern, D. *J. Org. Chem.* **1978**, *43*, 2480–2482.
21. Albright, J. D. *J. Org. Chem.* **1974**, *39*, 1977–1979.
22. All vinyl bromides were obtained by bromination of the parent 2-alkylidene-4-oxothiazolidines using molecular bromine.
23. Kuwajima, I.; Nakamura, E. In *Comprehensive Organic Synthesis*; Trost, B. M., Fleming, I., Heathcock, C. H., Eds.; Pergamon: Oxford, 1991; Vol. II, pp 441–473.
24. Negishi, E. *J. Organomet. Chem.* **1999**, *576*, 179–194.
25. *Typical experimental procedure for* **2a**: A solution of **1a** (49.0 mg, 0.16 mmol) in DMSO (2.9 mL) was heated in an oil bath at a temperature of 70 °C for 13 h. The red solution was cooled to rt, 20 mL of water was added and the product was extracted with AcOEt. The extract was evaporated under reduced pressure and the remaining liquid was purified by column chromatography (SiO_2, gradient toluene–AcOEt 7:3 to 1:1 v/v) to give *Z*+*E*-**2a** as a yellowish solid (32.2 mg, 63%). ^{1}H NMR (200 MHz, DMSO-d_6): (*Z* isomer) $\delta = 5.93$ (s, 1H, CHS), 7.14 (t, 1H, *p*-Ph, $J = 7.2$ Hz), 7.30–7.38 (m, 2H, *m*-Ph), 7.60 (d, 2H, *o*-Ph, $J = 7.6$ Hz), 9.48 (s, 1H, NH_{amide}), 11.29 (s, 1H, NH_{lactam}), (*E* isomer) $\delta = 5.69$ (s, 1H, CHS), 7.10 (t, 1H, *p*-Ph, $J = 7.4$ Hz), 7.28–7.36 (m, 2H, *m*-Ph), 7.60 (d, 2H, *o*-Ph, $J = 7.6$ Hz), 9.37 (s, 1H, NH_{amide}), 11.16 (s, 1H, NH_{lactam}). ^{13}C NMR (50.3 MHz, DMSO-d_6): (*Z* isomer) $\delta = 76.4$ (CHS), 85.3 (=CBr), 122.2 (*o*-Ph), 124.8 (*p*-Ph), 128.7 (*m*-Ph), 138.1 (C1-Ph), 150.8 (C=), 162.2 (CO_{amide}), 173.8 (CO_{lactam}), (*E* isomer) $\delta = 75.3$ (CHS), 81.2 (=CBr), 121.4 (*o*-Ph), 124.4 (*p*-Ph), 128.7 (*m*-Ph), 138.6 (C1–Ph), 148.1 (C=), 162.2 (CO_{amide}), 174.4 (CO_{lactam}). IR (KBr, *Z*+*E*): $\nu = 3313$, 3152, 3059, 1723, 1629, 1597, 1535, 1497, 1442, 1316, 1237, 1200, 862, 830, 772, 753, 691 cm^{-1}. CIMS: *m*/*z* 329/331 (M+1). UV (DMSO, *Z*+*E*) λ_{max} (ε) = 336.2 nm (11.900). Anal. Calcd for $C_{11}H_9BrN_2O_3S$: C, 40.14; H, 2.76; N, 8.51; S, 9.74. Found: C, 40.22; H, 2.76; N, 8.44; S, 9.47.
26. Marković, R.; Baranac, M.; Džambaski, Z. *Heterocycles* **2004**, *63*, 851–860.
27. Sandström, J. *Top. Stereochem.* **1983**, *14*, 83–181.
28. There is also a steric effect, due to the bulk of an acceptor substituent, which facilitates the C–Br bond cleavage—*unpublished data*.
29. Johnson, A. P.; Pelter, A. *J. Chem. Soc.* **1964**, 520–522.
30. Pfitzner, K. E.; Moffatt, J. G. *J. Am. Chem. Soc.* **1965**, *87*, 5661–5670.
31. De Luca, L.; Giacomelli, G.; Porcheddu, A. *J. Org. Chem.* **2001**, *66*, 7907–7909.
32. Alternatively, direct hydrolysis **11**→**2** may occur in the presence of water, preceding the formation of **12**.
33. Aida, T.; Akasaka, T.; Furukawa, N.; Oae, S. *Bull. Chem. Soc. Jpn.* **1976**, *49*, 1117–1121.
34. Aida, T.; Furukawa, N.; Oae, S. *Tetrahedron Lett.* **1973**, 3853–3856.
35. Since DMSO was a solvent in these reactions and was not dried prior to use, it contained the necessary amount of water for the beginning of the reaction.
36. Marković, R.; Baranac, M. *Synlett* **2000**, 607–610.
37. Marković, R.; Džambaski, Z.; Baranac, M. *Tetrahedron* **2001**, *57*, 5833–5841.